REMARKS

Rejection of Claims 1-7, 9, 10, 37-57 Under 35 U.S.C. §112, First Paragraph (Enablement)

Claims 1-7, 9, 10, 37-57 are rejected under 35 U.S.C. 112, first paragraph, for lack of enablement. The Examiner maintains that the field of the invention is unpredictable and that the Specification does not provide adequate teaching for one of ordinary skill in the art to make or use the broad scope of the invention absent undue experimentation.

Applicants reiterate their position that the specification for the above-identified application provides a substantial amount of guidance regarding how to make antibodies commensurate in scope with the claimed invention. The Specification describes the preparation of immunizing antigen and antibody production generally (page 13, line 24 through page 15, line 2) using well known methods, as well as describing the production of stable transfectants expressing high levels of CCR2 and use of these transfectants as immunogen (page 44, line 10 through page 49, line 8) to produce anti-CCR2 antibodies. As discussed more fully below, the use of these transfectants as immunogen permits the generation of antibody which may have an epitopic specificity for *any* available region of the protein. The Specification further describes the screening procedures for identifying antibodies which selectively bind CCR2 from the supernatants produced by the immunization techniques (page 49, line 1 through page 50, line 14). The Specification further discloses the methods by which an anti-CCR2 antibody can be identified as inhibiting binding of a ligand to CCR2 (page 20, line 27 through page 22, line 19 and page 50, lines15-28). As a result of the procedures outlined in the Specification, Applicants identified two anti-CCR2 antibodies which inhibit binding of a ligand to CCR2. It is clearly no more than routine procedure for one of skill in the art to follow the procedures described in the Specification to identify other antibodies which bind CCR2 and inhibit binding of a ligand to the receptor. The screening of even a large number of supernatants generated by an immunization protocol to identify antibodies having particular properties is clearly not undue experimentation, as such screening is practiced routinely in the art.

The Examiner has made a number of statements in response to Applicants' arguments submitted in the Amendment mailed to the Patent Office on May 8, 2003, and Applicants repond to these statements below.

First, the Examiner reminds Applicants that CCR2 is a G protein-linked seven transmembrane protein and asserts that making antibodies against such proteins is not routine since the various domains are internal (embedded in lipid membrane or internally within the cell). Applicants acknowledge that CCR2 is indeed a 7 transmembrane spanning G protein-

coupled receptor. However, in addition to the extracellular amino-terminal domain, CCR2 also comprises three extracellular loops which are clearly not internal and are therefore available for binding to antibody. Indeed, this position is supported by the work of Frade *et al.* cited against the subject application; Frade *et al.* demonstrate production of antibody which binds to the third extracellular domain of CCR2. Thus, there are at least three other domains of CCR2 in addition to the amino terminal domain which are not prevented from binding to antibody by virtue of being transmembrane or internal domains. Moreover, there are numerous examples of the generation of antibodies which recognize G protein-coupled receptors in the art (see, for example, U.S. Patent No. 5,440,021; U.S. Patent No. 5,994,515; Wu *et al.*, *J. Exp. Med. 185*(9): 1681-1691 (1997); and Ponath *et al.*, *J. Exp. Med. 183*:2437-2448 (1996), submitted herewith as Exhibits A-D, respectively). Thus, the mere fact that CCR2 is a G protein-coupled transmembrane receptor does not negatively impact the enablement of the subject application for the production of antibodies which bind CCR2 domains other than the amino-terminal domain and which inhibit binding of ligand to receptor.

The Examiner further states that in the Declaration Under 37 C.F.R. §1.131 ("Declaration") filed previously in the subject application, Applicants only raised antibodies against the amino-terminal region and primarily targeted their efforts toward the amino-terminal region. The Examiner alleges that Applicants targeted the amino-terminal domain of the protein and did not target other regions because to do so would require undue experimentation.

These statements are not supported by the Declaration. The successful immunization protocol evidenced by the Declaration comprised repeated immunization and boosting with both synthetic peptide immunogen and multiple cell lines transfected with intact CCR2 receptor and was *not* designed to produce antibodies directed at any *particular* domain of the protein. Previous immunization protocols utilizing synthetic peptides derived from the amino-terminus of CCR2 produced anti-CCR2 antibody 5A11 which did not inhibit binding of ligand to receptor. The use of whole cells transfected to express high levels of CCR2 receptor as immunogen increased the likelihood that antibodies generated by the immunized animal would recognize the receptor as expressed on the cell surface but did not allow the selection of the epitope to which antibody would bind (in contrast to the use of peptide immunogens). The Examiner states that if "making antibodies against all regions were as easily achievable as applicants now have the Office believe, then they would have directed their efforts to all regions". In fact, that is exactly the case; Applicants immunization protocol sought to obtain antibodies without regard for the region of the protein to which they bound, and Applicants thus did indeed direct their efforts to all regions of the protein which are capable of recognition by antibody.

Finally, the Examiner comments that the specification provides no teaching that other antibodies raised against any other regions except the amino-terminal region would provide the inhibition of ligand to receptor, and that such antibodies might not be capable of inhibiting (and might actually induce) signalling activity. The Examiner states that Applicants have taught raising antibodies against the N-terminal region and no other regions.

Applicants note that inhibition of functional activity of the receptor (e.g., signalling activity) is not a required characteristic of the claimed antibody. Furthermore, it is respectfully submitted that the Examiner appears to be confusing the lack of working examples of antibodies other than those which bind to the amino-terminal domain with lack of enablement for antibodies which bind to other domains fo the protein. This is simply incorrect, as there is no requirement for working examples to support the claims. *In re Robbins*, 166 USPQ 552 (CCPA 1970). Moreover, Applicants need not make and test all of the species within the scope of a generic claim. *In re Angstadt*, 190 USPQ 214 (CCPA 1976). 35 U.S.C. §112, first paragraph requires no more than a disclosure sufficient to enable one skilled in the art to carry out the invention commensurate with the scope of the claims, and this requirement has clearly been met. Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 1-7, 9, 10, 37-57 Under 35 U.S.C. §112, First Paragraph (Written Description)

Claims 1-7, 9, 10, 37-57 are rejected under 35 U.S.C. 112, first paragraph, for lack of written description. The Examiner maintains that Applicants were not in possession of antibodies against all other regions within the seven transmembrane protein of CCR2.

Applicants continue to respectfully traverse this rejection. It is incorrect to characterize the application as disclosing only antibodies which bind to the amino-terminal domain of CCR2, as the application is replete with a broader description of Applicants' invention. It appears that the Examiner has improperly limited the alleged disclosure of the application to the working examples disclosed therein. Applicants acknowledge that the two working examples provided in the application relate to antibodies (1D9 and 8G2) which bind the amino-terminal domain of CCR2. However, the "disclosure" of a patent application is not limited to the working examples but rather encompasses all of the teachings of the application. In addition, "possession" does not require an actual reduction to practice; rather, an applicant can show possession of the claimed invention by describing it with all of its limitations using such descriptive means as words, structures, figures, diagrams and formulas that fully set forth the invention. *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997).

Applicants provide a clear description with all of the limitations of one aspect of their invention as an antibody which binds CCR2 (page 10, lines 10-11) and inhibits binding of a ligand to the receptor (page 10, lines 27-28) and have reduced to practice two embodiments which meet all of the limitations, e.g., of Claim 1.

The Examiner provides a number of statements relating to the prosecution of the parent application (U.S. Patent No. 6,312,689) and the alleged grounds for allowance of that patent. Applicants believe that these statements are not relevant to the written description of the current claims, as the claims at issue are different from the granted claims in the parent application and must be addressed on their own merit. Moreover, as an aside, Applicants note that when claims of similar scope to those currently pending were presented in the parent application, there were no rejections under 35 U.S.C. §112 made (other than a requirement for a biological deposit with regard to claims reciting the particular antibody species).

The Examiner also mischaracterizes the Declaration in the context of this rejection as evidence that applicants were not in possession of antibodies against any and all regions of CCR2 because Applicants "targeted" their efforts to raising antibodies and the amino-terminal domain. Again, Applicants reiterate that their efforts were directed to producing antibodies which bound CCR2 and inhibited binding of ligand to CCR2; the first antibodies which resulted from these efforts with the desired properties bound to the amino-terminal domain.

For original claims, as is the case here, there is a strong presumption that an adequate written description of the claimed invention is present when the application is filed. *In re Wertheim*, 191 USPQ 90 (CCPA 1976). Applicants provide a clear description that their invention encompasses an antibody which binds CCR2 (page 10, lines 10-11) and inhibits binding of a ligand to the receptor (page 10, lines 27-28) and have reduced to practice two embodiments which meet all of the limitations, e.g., of Claim 1. Thus, it must be said that the Specification demonstrates that Applicants were in possession of the claimed invention at the time the application was filed. Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 1, 9, 44 and 52 under 35 U.S.C. §101 (Double Patenting)

Claims 1, 9, 44 and 52 are provisionally rejected as claiming the same invention as that of claims 1 and 6 of copending Application No. 09/840,459. Applicants note that the Examiner has indicated that the rejection will be maintained until such time as no conflicting claims remain or a Terminal Disclaimer is submitted. Applicants also note that a Terminal Disclaimer cannot overcome a "same invention" type double patenting rejection based on 35 U.S.C. §101. *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970) and MPEP §804.

However, upon further review it is clear that Claims 1, 9, 44 and 52 do not claim the same invention as that of claims of copending Application No. 09/840,459. A reliable test for double patenting under 35 U.S.C. §101 is whether one claim could be literally infringed without literally infringing the corresponding claim alleged to be the same invention. *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970) and MPEP §804. If an embodiment exists which is within the scope of one claim but not the other, then identical subject matter is not defined by both claims and statutory double patenting would not exist. Application of this test clearly shows that there are embodiments which would fall within the scope of Claims 1, 9, 44 and 52 of the current application which would not be within the scope of the claims of copending Application No. 09/840,459. If this rejection is maintained, the Examiner is respectfully requested to clarify the claims of copending Application No. 09/840,459 which form the basis for the provisional rejection, as the claims of the copending application have been amended since the first presentation of this provisional rejection.

Rejection of Claims 1-7, 9, 10 and 37-57 under 35 U.S.C. §102(e)

Claims 1-7, 9, 10 and 37-57 are rejected under 35 U.S.C. 102(e) as being clearly anticipated by Lind, *et al.* (U.S. Patent No. 6,084,075). The Examiner notes that the submission of the Declaration is not sufficient to antedate the patent to Lind *et al.* because the rejection is made over the claims and disclosure of the patent, and that the claims of the patent to Lind *et al.* anticipate the broad limitations of the claimed invention. Thus, it appears that the Examiner has determined that Lind *et al.* is a patent claiming the same invention as the subject application, and may be suitable for an interference proceeding.

It is noted that 37 C.F.R. §1.606 requires that before an interference is declared between and application and an unexpired patent, the Examiner must determine that there is interfering subject matter claimed in the application and that patent which is patentable to the applicant subject to a judgment in the interference. Moreover, MPEP §2306.01 makes clear that an interference between an application and a patent cannot be declared if the patent is a reference against the application under 35 U.S.C. §§102(e)/103, unless Applicant has filed a showing under 37 C.F.R. §1.608. It is Applicants' understanding that prior to a declaration of interference there must first be an indication of allowable claims in the subject application, followed by a showing by Applicants under 37 C.F.R. §1.608. Accordingly, it is believed that further action relating to this rejection may be held in abeyance until allowable subject matter is indicated. If this understanding is incorrect, Applicants respectfully request clarification from the Examiner.

Rejection of Claims 1-7, 9, 10 and 37-57 under 35 U.S.C. §102(a)

Claims 1-7, 9, 10 and 37-57 are rejected under 35 U.S.C. 102(a) as being anticipated by Frade *et al.* (J. Clin. Invest. 1997; "Frade 1"), Frade *et al.* (J. Immunology, 1997; "Frade 2"), and Lind *et al.* (WO 97/31949, 9/4/1997). The Examiner states that the Declaration is not deemed sufficient to overcome these rejections because it does not evidence either conception or reduction to practice of antibodies or fragments directed against all regions of CCR2. Specifically, the Examiner states that the laboratory notes submitted as exhibits to the Declaration show experiments and efforts directed toward raising antibodies against the amino-terminal region only.

Applicants respectfully traverse this rejection. First, Applicants note, as detailed more fully above in response to the rejection under 35 U.S.C. §112, first paragraph (enablement), the Examiner's statement that all of Applicants' efforts were directed toward raising antibodies against the amino-terminal domain is a mischaracterization of the facts evidenced by the Declaration. Applicants efforts were directed to making antibodies which bind CCR2 and inhibit binding of ligand to CCR2; as it turned out, the first such antibody identified bound the amino-terminal domain of CCR2.

Furthermore, regardless of the Examiner's perception of the direction or goals of Applicants' work, the fact remains that the conception and diligent reduction to practice of an antibody which binds CCR2 and inhibits binding of ligand to CCR2 is evidenced by the Declaration; the Examiner does not dispute this point. Rather, the Examiner believes that conception and diligent reduction to practice of an antibody which binds the amino-terminal domain of CCR2 and inhibits binding of ligand to CCR2 is not sufficient to demonstrate prior invention of the claimed antibody genus.

However, the law is clear on this point. A reference applied against a generic claim may be antedated as to such claims by a Declaration under 37 C.F.R. §1.131 showing prior invention of only a single species within the genus prior to the effective date of the reference. If the teachings of Frade 1, Frade 2 or Lind *et al.* are deemed to disclose the claimed genus, then it is well-settled that a showing of prior invention of a single species within the genus is sufficient to antedate the reference. *Ex parte Biesecker*, 144 USPQ 129 (Bd. App. 1964). Alternatively, if Frade 1, Frade 2 or Lind *et al.* are deemed to disclose multiple species, a showing of prior invention of one or more species which put Applicant in possession of the claimed genus is sufficient to antedate the reference. All that is required is that the prior species provide an adequate basis for inferring that the invention has generic applicability. *In re Plumb*, 470 F.2d 1403, 176 USPQ 323 (CCPA 1973); *In re Rainer*, 390 F.2d 771, 156 USPQ 334 (CCPA 1968);

In re Clarke, 356 F.2d 987, 148 USPQ 665 (CCPA 1966); *In re Shokal*, 242 F.2d 771, 113 USPQ 283 (CCPA 1957). That is, the Declaration must show as much as the minimum disclosure required by a patent specification to furnish support for a generic claim.

It is quite clear from the evidence provided in the Declaration and the discussion above relating to the enablement of the claimed invention that the Declaration does indeed establish that the species for which Applicants have shown prior invention provides an adequate basis for inferring that the invention has generic applicability. Applicants have demonstrated conception of the claimed generic invention by providing evidence of an intention and a plan to obtain antibodies which bind to CCR2 and inhibit binding of ligand to CCR2, and have further evidenced a diligent execution of that plan leading to a reduction to practice of at least one species fulfilling all of the requirements of the generic claim. Furthermore, the methods used by Applicants as described in the application and evidenced in the Declaration are broadly applicable to obtain additional antibodies within the scope of the claim and are not limited, as the Examiner alleges, to the production of antibodies which bind the amino-terminal domain of CCR2. Accordingly, the Declaration is legally sufficient to antedate the disclosure of Frade 1, Frade 2 and Lind *et al.* Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 44-57 Under 35 U.S.C. §112, Second Paragraph

Claims 44-57 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. The Examiner maintains that the phrase "antigen-binding fragment" is indefinite. Applicants respectfully submit that the Examiner appears to be under the misimpression that the phrase relates to a portion of the CCR2 receptor which is bound by antibody. However, the claim clearly recites that the antigen-binding fragment is a fragment *of the antibody*, not the receptor. Applicants believe that this clarification obviates all of the issues raised in this regard. Particular fragments of antibodies which are capable of binding to antigen are known in the art and are exemplified in the Specification (for example, page 15, lines 3-24), and this term is indeed definite to one of skill in the art. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned at (978) 341-0036.

Respectfully submitted,

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Exhibit A: U.S. Patent No. 5,440,021
Exhibit B: U.S. Patent No. 5,994,515
Exhibit C: Wu *et al.*, *J. Exp. Med. 185*(9): 1681-1691 (1997)
Exhibit D: Ponath *et al.*, *J. Exp. Med. 183*:2437-2448 (1996)